REMARKS

Claims 1-8, 10, and 12-17 were pending in the present application. Claims 1, 4, 6-7, and 16-17 have been amended. Claims 5, 8, and 12-15 have been canceled, and new claims 18-28 have been added. Support for the amended and new claims can be found throughout the specification and original claims, for example, at pages 13, line 28, through page 45, line 1 (Examples 1-79); and page 1, line 6 (depression). No new matter has been added. Upon entry of the present amendment, claims 1-4, 6-7, 10, and 16-28 will be pending.

As a preliminary matter, Applicants acknowledge with gratitude the withdrawal of the written description rejection of claims 1 and 7-9, and the withdrawal of the objections to the specification.

I. Interview

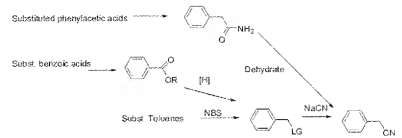
Applicants note with gratitude the courtesies extended Applicants' representative, Susanne Goodson, during a telephonic interview with Examiner O'Dell on October 12, 2007. The enablement rejection regarding how to make the claimed compounds was discussed, including the various synthetic routes into the phenylacetonitrile starting materials, as well as possible amendments to R^4 and R^1, particularly in light of the Raney nickel hydrogenation synthetic step. Examiner O'Dell agreed to consider withdrawing the enablement rejection of the compound claims if particular amendments were made to R^4 and R^1, and substituents defined therein. The amendments and remarks submitted herewith are consistent with the interview.

With respect to the method claims, the implications of the McLean reference were discussed, including the clinical trials demonstrating the antidepressant activity in mildly depressed and melancholic patients. Applicants' representative pointed to the Papp and Santarelli articles cited in Applicants' specification in support of a link between NK_1 antagonists and the treatment of anxiety and depression (page 1, line 30, through page 2, line 2). Further, Applicants' representative noted that NK_1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies as summarized in the Rosenzweig-Lipson article. Examiner O'Dell agreed to reconsider the enablement of the method claims directed to depression and anxiety. He also agreed to issue an advisory action to Applicants' response. The amendments and remarks submitted herewith are consistent with the interview.

II. The Claims are Enabled

Claims 1-3, 5-7, and 12-14 are been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the enablement requirement. In particular, the Office alleges that a person skilled in the art would know how to make the claimed compounds. As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). Applicants respectfully assert that undue experimentation would not be required to make the claimed compounds.

The Office has alleged that "[t]he applicant needs substituted benzyl nitriles...and no guidance has been given as to how one might arrive at these compounds" (Final Rejection, page 7). Applicants, however, note that a number of substituted phenylacetonitriles have been available since the effective date of this application (for a non-limiting number of examples, please see, e.g., Aldrich Catalog Handbook of Fine Chemicals (1998-1999), pages 66, 550, 590, 1069, 1088, 1657, and 1661). Further, as discussed during the interview, there are a variety of common synthetic routes to these materials, as illustrated below. For example, one route to nitriles is a simple substitution reaction of a benzyl compound with a cyanide ion (see e.g., US3940402 (issued 1976); Regen, *J. Org. Chem.* 42(5):875-9 (1977); Cao, et al., *Synth. Commun.* 31(14):2203-2207 (2001); US4165372 (issued 1979)). The substituted benzyl alcohols are available commercially or can be synthesized from ubiquitous starting materials, such as substituted benzoic acids or substituted toluenes (see e.g., Singh, et al., *Proceed. Intern. Zeolite Conf., 12th, Baltimore, July 5-10, 1998* (1999)). Alternatively, another common route to nitriles is the dehydration of a phenylacetamide, which can be derived from a phenylacetic acid (see e.g., Bose and Kumar, *Synth. Commun.* 30(16):3047-3052(2000); and Bose and Sunder, *Synth. Commun.*, 29(23):4235-4239 (1999)). Accordingly, Applicants respectfully assert that undue experimentation would not be required to make the "substituted benzyl nitriles".



The Office has further alleged that many of the compounds "will not participate in the synthesis given [in the Office's Scheme 1]" (Final Rejections, page 8). In particular, the Office alleges that, where "R^4 is a nucleophile such as NR^aR^b, $CH_2R^aR^b$, SR^a, CH_2OR^a, OR^a, $C(O)R^a$, [it] will attack the dichloride..., preferentially leading to other products" (Final Rejection, page 8). In particular, the Office alleges that certain groups for R^4 are not enabled "due to the use of Raney Ni/H_2" to make some of the compounds of the Examples. While Applicants maintain these deficiencies could be overcome by reasons already of record, the claims have been amended solely to advance prosecution. For the remaining groups, Applicants respectfully assert that these nucleophilic groups can be protected by the use of protecting groups, as delineated *infra*.

(A) $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, wherein G is oxygen or sulfur. The Office alleges that this group is not enabled, because "[g]roups that contain sulfur will undergo desulfurization" (Final Rejection, page 8). While Applicants respectfully assert that this could be overcome by use of lithium aluminum hydride, "$G(CH_2)_jG$" has been canceled from the definition of R^a and R^b, and "sulfur" has been deleted from the definition of G, solely to advance prosecution.

(B) Nitrile (CN). While Applicants maintain that the cyano group could be introduced by known electrophilic substitution reactions starting from compound 6 of the Office's Scheme 1, "CN" has been deleted from the definition of R^4, solely to advance prosecution.

(C) Alkenes and alkynes. While Applicants respectfully assert that this could be overcome by use of lithium aluminum hydride, "C_{2-4}alkenyl and C_{2-4}alkynyl" have been canceled from the definition of R^4, solely to advance prosecution.

(D) Ketones and aldehydes. Applicants respectfully assert that there are a number of groups for protecting ketones and aldehydes, including dimethyl acetals, dimethyl ketals and bismethylenedioxy derivatives, which render these groups stable to hydrogenation using Raney nickel (Greene's Protecting Groups in Organic Synthesis, 4th ed., pages 1009-1012).

(E) *o*-Halogen and other halogens. The Office alleges that "upon reduction of the ntirile an intromolecular cyclization will occur to give spirocyclic indolo-piperidines as taught by Ong" (Final Rejection, page 9). Applicants respectfully disagree and direct the Office's attention to the cited Ong reference, wherein attempts to effect reductive cyclization of 2a with lithium aluminum hydride yielded both a cyclized and non-cyclized product (Ong, *J. Med. Chem.* **1983**, 26, 981-986, at page 981). The Ong reference further reports recrystallization of the crude non-cyclized product (Ong, at 984). Accordingly, one of skill in the art would be able to prepare the non-cyclized product when R^4 is halogen in the *o*-position of the phenyl ring without undue experimentation.

The Office further notes that "Raney/Ni will dehalogenate aryl halides, resulting in a what is formally a replacement of halogen with hydrogen" (Final Rejection). However, the Office appears to concede that "applicant seems to have provided conditions that prevent this reaction" (Final Rejection, page 9). Indeed, Applicants' specification is replete with examples showing the use of halogenated phenylacetonitriles (*see e.g.*, Examples 1-18). Accordingly, Applicants respectfully assert that one skilled in the art would be able to prepare the halogenated compounds without undue experimentation.

(F) The Office further alleges that "[a]pplicant makes claims to compounds where R^2 is other than H...and no guidance is provided as to how we can arrive at these compounds" (Final Rejection, page 10). The Office further notes that it "would seem that a starting material as shown in Scheme 1, is required, yet we do not have any guidance as to how may obtain such compounds" (Final Rejection, page 10). Applicants respectfully direct the Office's attention the preparation of the compound of Example 1, wherein R^2 is methyl. Moreover, compound 4 of the Office's Scheme 1 can be alkylated by using an alkyl halide. The feasibility of this type of reaction chemistry has been demonstrated in the preparation of Applicants' working examples, albeit for R^3 (see e.g., Example 7, reacting the piperidine amino group with 2-bromoethyl methyl ether). This process is generally applicable to compounds where R^2 is C_{1-6}alkyl or C_{1-6}alkyl substituted with C_{1-4}alkoxy, as recited by claim 1.

(G) The Office further alleges that "naphthoic acids...required for the scope of this invention are not commerical", but concedes that "applicant makes reference to a prior commonly assigned application for a good portion of these and these will be considered allowable" (Final Rejection, page 11). Applicants respectfully disagree that a variety of 1-

naphthoic acids (as well as 1-naphthaldehydes and 1,8-naphthalic anhydrides, which can be converted easily to 1-naphthoic acids by oxidation or hydrolysis) are not commerically available (for a non-limiting number of examples, please see, e.g., Aldrich Catalog Handbook of Fine Chemicals (1998-1999), pages 261, 624, 634, 818, 930, 1066, and 1185). Further, Applicants respectfully note that the naphthoic acid is used in nearly the last step of the process, involving amide formation between the naphthoic acid and the primary amine of compound 4 of the Office's Scheme 1. Very few functional groups will interfere with this step. Moreover, as delineated above, there are a variety of protecting groups known that can protect various functional groups on the naphtoic acid, including aldehyde, ketone, amino, and hydroxyl groups (*vide supra*).

The Office further speculates as to: "[w]hat are the effects of these long alkyl chains or 10 sulfur atoms? We do not know but in this case the members of the genus bear no structural resemblance to one another and even if they did the situation is far from clear that they would have the desired activity" (Final Rejection, page 11). While Applicants maintain that sulfur containing moieties would possess the desired activity, sulfur containing moieties, including SR^a have been deleted from the definitions of R^1 and R^4, and sulfur has been deleted from the definition of G. Further, Applicants respectfully note that the alkyl groups in the compounds of Formula have up 6 carbon atoms, which is reasonable in light of the number of working examples having alkyl and alkoxy groups (see e.g., Examples 4, 9, 19, 20, 27, and 70).

For all of the reasons summarized herein, Applicants respectfully assert that undue experimentation would not be required to make the compounds of the invention and request that the claim rejections be withdrawn.

Claims 8-10 are rejected as allegedly failing to meet the enablement requirement. In particular, the Office alleges that a person skilled in the art would know how to use the claimed methods. While conceding that the Ryckmans article "suggests that these kinds of compounds might be useful for the treatment of depression and they may well be", the Office asserts that the Rosenzwieg-Lipson article suggests that "the state of the art in the area of these dual antagonists is murky at best" (Final Rejection, page 14). The Office further asserts that "even if these compounds were evaluated simply as NK_1 antagonists" that it would "unlikely that one of skill in

the art would know what to do with these compounds", based on failed trials in the McLean article (Final Rejection, pages 14-15). Applicants respectfully disagree.

As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971) (emphasis added). Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

As a preliminary matter, claim 8 has been canceled and claim 10 has been amended to recite only methods of treating various forms of depression. Further, new claims 16-23 and 27-28 have been added, reciting methods of treating generalized anxiety disorder and various forms of depression.

The Office has not carried its burden under *In re Marzocchi*. Further, the claimed methods can be used without undue experimentation. As asserted by Applicants' specification, the compounds have both NK_1 antagonist and serotonin reuptake inhibitory (SRI) activity. There is ample evidence of the efficacy of NK_1 antagonists and SRI's for treating depression and anxiety. For example, the McLean article summarizes the results of 19 positive preclinical studies showing the anxiolytic effect of NK_1 antagonists and 14 positive studies showing the antidepressant effect of NK_1 antagonists, all published prior to the filing date of this application (McLean, Table 2, pages 1536-37). The anxiolytic and antidepressant effect of NK_1 antagonists is further supported by the articles cited by Applicants' specification, showing the involvement of NK_1 receptors in depression and a decrease in the anxiety behavior of mice following administration of NK_1 antagonists (Papp, et al., Behav. Brain Res. 115:19 (2000); and Santarelli, et al., Proc. Nat. Acad. Sci. 98:1912 (2001); cited in the specification at page 1, line 30, through page 2, line 2). Moreover, serotonin reuptake inhibitors were well-known to have efficacy in treating anxiety and depression (Boerner and Moeller, Pharmacopsychiatry, 32(4):119-26 (1999)). Hence, there is a clear link between the treatment of depression and anxiety and NK_1 antagonist and serotonin reuptake inhibition activity. Accordingly, one of skill in the art would be able to practice the claimed methods of treating depression and generalized anxiety disorder without undue experimentation.

In light of this evidence, the sections of Rosenzwieg-Lipson and McLean fail to provide sufficient evidence to doubt the enablement of the claimed methods, as amended. As to McLean, the Office points to a statement in the article that "[t]o date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies" (Final Rejection, page 14; McLean, page 1542). However, in the supposed "failed" trial for MK-869, a dose dependent decrease in depression symptoms in subjects was observed, leading the reviewers to suggest that MK-869 would actually be effective for subjects with greater depression (McLean, page 1541). In the single negative trial for MK-869, McLean indicates that the report was gleaned from the "lay press" and that "details were not available" (McLean, page 1541). Similarly, in the negative trial for L-75927, McLean indicates that the response to paroxetine-which is indicated for depression-also failed to distinguish from placebo (McLean, page 1541). Hence, the reliability of both "negative trials" is questionable. Further, Applicants respectfully assert that clinical trials may fail for a variety of reasons, including safety concerns

which are outside the purview of the U.S. Patent and Trademark Office. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Moreover, McLean does not take into account the effect of serotonin reuptake inhibitory activity.

Rosenzwieg-Lipson actually suggests that compounds with combined NK_1 antagonist and serotonin reuptake inhibitory activity would have potentiated antidepressant activity. For example, while Rosenzwieg-Lipson summarizes the failure of one Phase III depression trial for a single NK_1 aprecpitant adminstered alone, it also states that "NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies" (Final Rejection, page 14; Rosenzwieg-Lipson article, page 140). Hence, Rosenzwieg-Lipson supports the enablement of the claimed methods.

In light of the foregoing discussion, Applicants respectfully assert that methods of claims 10, 16-23 and 27-28 meet the requirements of 35 U.S.C. § 112, first paragraph, and request the claim rejections be withdrawn.

III. Conclusion

Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7854 to resolve any remaining issues.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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